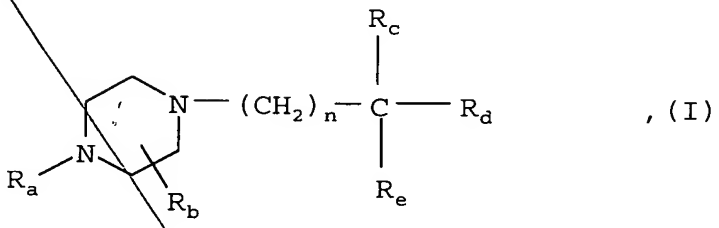
Patent Claims

1. Substituted piperazine derivatives of general formula



, (I)

wherein

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, a hydroxy, C_{1-4}-alkoxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkyl-carbonyl-amino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkyl-sulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group or

R_1 and R_2 together denote a methylenedioxy group,

a heteroaryl group,

a monocyclic heteroaryl or phenyl group each of which is substituted by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl moieties may each be substituted by a fluorine, chlorine or bromine atom and the abovementioned phenyl moieties and heteroaryl groups may each be substituted by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_c denotes a hydrogen atom,

a C_{1-10}-alkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group wherein the hydrogen atoms in each case may be wholly or partially replaced by fluorine atoms,

a phenyl, naphthyl or heteroaryl group optionally substituted by a fluorine, chlorine or bromine atoms, by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group,

R_d denotes a phenyl, naphthyl or heteroaryl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, and

R_e denotes a carboxy group, a C_{1-6}-alkoxycarbonyl or C_{3-7}-cycloalkoxycarbonyl group, wherein the carbon atom of the alkoxycarbonyl group linked to the oxygen atom is a primary or secondary carbon atom and wherein the alkyl or cycloalkyl moiety of both groups may be substituted from position 2 in relation to the oxygen atom by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxycarbonyl or heteroaryl-C_{1-3}-alkoxycarbonyl group,

while the abovementioned heteroaryl groups are 6-membered heteroaryl groups containing one, two or three nitrogen atoms, and 5-membered heteroaryl groups, containing an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms,

the isomers and the salts thereof.

2. Substituted piperazine derivatives of general formula I according to claim 1, wherein

R_e is defined as in claim 1,

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, while

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy, benzyloxy, carboxy, C_{1-3}-alkyloxycarbonyl, nitro, amino, acetamino or methanesulphonylamino group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group or

R_1 and R_2 together denote a methylenedioxy group,

a biphenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,

a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or

a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl group or benzimidazolyl group,

R_b denotes a hydrogen atom,

R_c denotes a C_{1-3}-alkyl or phenyl group and

R_d denotes a phenyl group optionally substituted by a fluorine or chlorine atom or a methyl or methoxy group,

the isomers and the salts thereof.

3. Substituted piperazine derivatives of general formula I according to claim 1, wherein

R_e is defined as in claim 1 or 2,

n denotes the number 3 or 4,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy or benzyloxy group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group,

a biphenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,

a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or

a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl or benzimidazolyl group,

R_b denotes a hydrogen atom,

R_c denotes a C_{1-3}-alkyl group and

R_d denotes a phenyl group optionally substituted by a fluorine atom,

the isomers and the salts thereof.

4. The following substituted piperazine derivatives of general formula I according to claim 1:

(a) methyl 2-ethyl-2-phenyl-5-[4-(4-chloro-phenyl)-piperazin-1-yl]-pentanoate,

(b) methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate and

(c) methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate,

the isomers and the salts thereof.

5. Physiologically acceptable salts of the compounds according to claims 1 to 4.

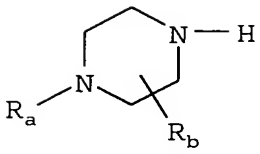
6. Medicaments, containing a compound according to at least one of claims 1 to 4 or a salt according to claim 5 optionally together with one or more inert carriers and/or diluents.

7. Use of a compound according to at least one of claims 1 to 4 or a salt according to claim 5 for the preparation of a medicament having a lowering effect on the plasma levels of atherogenic lipoproteins.

8. Process for preparing a medicament according to claim 6, characterised in that a compound according to at least one of claims 1 to 4 or a salt according to claim 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

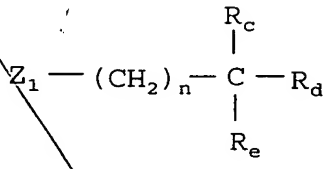
9. Process for preparing the compounds according to claims 1 to 5, characterised in that

a. a compound of general formula



, (II)

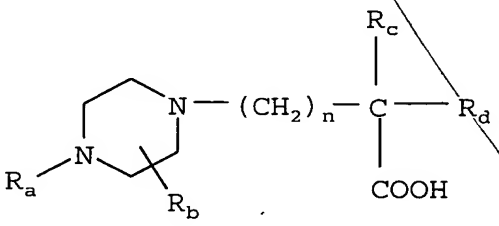
wherein
R_a and R_b are defined as in claims 1 to 4, is reacted with a compound of general formula



, (III)

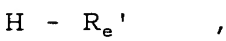
wherein
n and R_c to R_e are defined as in claims 1 to 4 and
Z_1 denotes a nucleofugic leaving group, or

b. to prepare a compound of general formula I wherein R_e has the meanings mentioned for R_e in claims 1 to 4 with the exception of the carboxy group,
a compound of general formula



, (IV)

wherein
n and R_a to R_d are as defined in claims 1 to 4, or the reactive derivatives thereof, is esterified with an alcohol of general formula



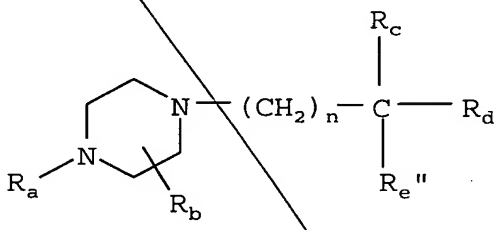
, (V)

wherein

R_e' denotes a C_{1-6}-alkoxy or C_{3-7}-cycloalkoxy group wherein the alkyl or cycloalkyl moiety may in each case be substituted from the 2 position, relative to the oxygen atom, by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxy or heteroaryl-C_{1-3}-alkoxy group, while the heteroaryl moiety is as hereinbefore defined, or

a tert.butyl ester is prepared by reacting with 2,2-dimethyl-ethene in the presence of an acid or

c. in order to prepare a compound of general formula I wherein R_e denotes a carboxy group, a compound of general formula



, (VI)

wherein
n and R_a to R_d are as defined in claims 1 to 4 and
R_e" denotes a group which can be converted into a carboxy group, is converted into a compound of general formula I wherein R_e denotes a carboxy group, and

subsequently, if desired, a compound of general formula I thus obtained which contains a nitro group is converted by reduction into a corresponding amino compound and/or

a protecting group used during the reactions to protect reactive groups is cleaved and/or

a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use

into the physiologically acceptable salts with an inorganic or organic acid or base.

add a'